REMARKS

The remainder of this Reply is set forth under appropriate subheadings for the convenience of the Examiner.

Amendments to Claims

Claims 19, 28 and 34-37 have been amended to more clearly define Applicant's claimed invention. Support for amendments to the claims can be found in the specification. For example, page 4, lines 26-27 and page 17, lines 11-12 describes a polymer component having an aqueous solubility of at least one mg/liter at 25°C, thereby providing support for the amendment to Claim 34; and page 10, lines 26-28 describe the reversible association between a drug and a nucleotide as a noncovalent association, thereby providing support for amendments to Claims 35-37.

The amendments to claims do not add new matter. Entry is requested.

Claim 35

Claim 35 was not rejected. Applicant requests an indication of allowance of Claim 35 or a clarification of the status of Claim 35.

Rejection of Claims 14-16, 20-22, 34, 36 and 37 under 35 U.S.C. §102(b)

Claims 14-16, 20-22, 34, 36 and 37 are rejected under 35 U.S.C. §102(b) as being anticipated by PCT Application No. PCT/US98/25,650 by Warren, S. (hereinafter "Warren"). In particular, the Examiner stated that Warren teaches drug carriers comprising a nucleotide with less than 5% moisture content by weight, and further comprises a drug component which, optionally, further comprises a biocompatible polymer. The Examiner further stated that the nucleotide drug carrier component of Warren is either double or single stranded and the polymer of Warren, which is optionally covalently linked to the nucleotide, has an aqueous solubility of at least 1 mg/liter at 25°C. In addition, the Examiner stated that the drug carrier of Warren delivers a drug optionally comprising a nucleic acid or non-nucleic acid component.

As stated on page 16, lines 29-30, Warren discloses:

> nucleotide-based prodrugs comprising a nucleotide component covalently bonded to a drug component via a junctional ester bond.

(Emphasis added).

In addition, Warren states on page 19, line 28 through page 20, line 2:

> In embodiments wherein the pharmacologically active drug component of the nucleotide-based prodrug is covalently bonded to more than one nucleotide component, the release of the drug will be prolonged even further since release of the drug will require the hydrolysis of more than one junctional ester bond.

(Emphasis added).

As stated on page 17, lines 7-16 of Warren, release of the drug in the nucleotide-based prodrugs is achieved by hydrolysis of the ester bond between the drug component and nucleotide component of the nucleotide-based prodrug:

> Release of the active drug arises from hydrolysis of a junctional ester bond which joins the active drug component to the nucleotide component of the nucleotide-based prodrug. The present invention is based on the unique insight that the rate of release and activation of the drug can be manipulated by chemically altering the nuclease resistance of the nucleotide component of the nucleotide-based prodrug and/or chemically altering the nuclease resistance of the junctional ester bond joining the drug to a nucleotide component. Increasing the nuclease resistance of the nucleotide component will in turn decrease the rate of release of the active drug component of the nucleotide-based prodrug. In this way, versatile sustained release properties can be bestowed upon nucleotide-based prodrugs.

Further, as noted on page 19, lines 13-15 of Warren, *in vivo* hydrolysis of the ester bond between the nucleotide component and the drug component is required for release and activation of a drug component of the nucleotide-based prodrug .

> In the above embodiments, it is necessary that the junctional ester bond coupling the drug component to the nucleotide component of the nucleotide-based prodrug is able to be hydrolyzed *in vivo*.

(Emphasis added).

As stated by Warren on page 32, lines 5-19, the nucleotide component of the nucleotide based prodrug optionally has a covalently bonded macromolecular support, such as a biocompatible polymer.

Applicant's invention, as claimed in independent Claim 14, is a drug carrier comprising a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double stranded nucleotide, the polymer component having an aqueous solubility of at least one mg/liter at 25°C. Claims 15 and 16 are dependent from Claim 14 and add further limitations that the polymer is component is a biocompatible polymer component and is cross-linked, respectively. Claims 20-22 are dependent from Claim 14 and add further limitations that the polymer component includes at least one polymer, the polymer being covalently bonded to at least one strand of the nucleotide; that the polymer component includes at least two polymers; and that the polymer component includes at least two chemically distinct polymers, respectively.

There is no disclosure in Warren of a drug carrier comprising a double-strand nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide with the polymer component have an aqueous solubility of at least one mg/liter at 25°C. On page 32, lines 5-19, Warren describes the polymers of the nucleotide-based prodrugs to include polymers which are insoluble in an aqueous solution. Therefore, Warren does not expressly or inherently disclose Applicant's invention, as set forth in Claim 14, which employs a polymer having an aqueous solubility of at least about one mg/liter at 25°C. Claims 15, 16 and 20-22 are dependent from Claim 14. Therefore, Warren also does not disclose the subject matter of Applicant's Claims 14-16 and 20-22.

Applicant's Claim 34, as amended, is directed to a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, wherein the polymers have an aqueous solubility of at least one mg/liter at 25°C. Claim 36, as amended, is directed to a drug-carrier composition comprising a nucleotide carrier component and a drug component noncovalently associated with the nucleotide carrier component, the drug-carrier composition having a moisture content less than about 5% by weight. Claim 37, as amended, is directed to a drug-carrier composition consisting essentially of a drug component noncovalently associated with a nucleotide component.

As discussed above, there is no disclosure or suggestion in Warren of a drug-carrier comprising a single-stranded nucleotide and at least two polymers associated with the single strand nucleotide, wherein the polymers have an aqueous solubility of at least one mg/liter at 25°C, as set forth in Applicant's Claim 34, as amended. In addition, there is no disclosure or suggestion in Warren of a drug-carrier composition comprising a nucleotide carrier component and a drug component noncovalently associated with the nucleotide carrier component, the drug-carrier composition having a moisture content less than about 5% by weight, which is the subject matter of Claim 36, as amended. Further, there is no disclosure in Warren of a drug-carrier composition consisting essentially of a drug component noncovalently associated with a nucleotide component, as set forth Claim 37, as amended. As discussed above, Warren requires a covalent bond between the drug and the nucleotide component to form a hydrolyzable ester bond. Thus, Warren does not disclose Applicant's claimed drug-carrier, drug-carrier complex and drug-carrier composition, as set forth in amended Claims 34, 36 and 37 of Applicant's invention.

Therefore, the subject matter of Claims 14-16, 20-22, 34, 36 and 37 meet the requirements of 35 U.S.C. § 102 in view of Warren.

Rejection of Claims 14-17, 20-22, 28-30, 34, 36 and 37 under 35 U.S.C. § 103

Claims 14-17, 20-22, 28-30, 34, 36 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Warren and further in view of the combination of Matysiak, *et al.*, "Acetal Oligonucleotide Conjugates in Antisense Strategy," *Nucleosides and Nucleotides*, 16(5&6):855-861 (1997) (herein after "Matysiak, *et al.*"), U.S. 6,057,431, issued to Ishihara, *et al.*, (herein

after "Ishihara, *et al.*) and Gao, Q. *et al.*, "Drug-induced DNA repair: X-ray structure of a DNA-ditercalinium complex," *Proc. Natl. Acad. Sci. USA*, 88:2422-2426, March 1991 (herein after "Gao, *et al.*") and U.S. Patent No. 5,817,343 to Burke, P.A. (Hereinafter "Burke"). In particular, the Examiner stated that it would have been obvious to one of ordinary skill in the art to design and utilize drug-carriers comprising a nucleotide component and a biocompatible polyacetal component because drug carriers comprising nucleic acids and non-nucleic acid drugs, and optionally comprising polymers, have been taught by Warren, and drug-carrier complexes have been successfully designed and utilized for the target cell delivery of various agents including labile drug delivery, as taught by Burke. In addition, the Examiner stated:

> One of ordinary skill in the art would have expected that nucleic acid components are used for cellular delivery of both nucleic acid and non-nucleic acid drug delivery because such drug carriers have been taught previously by Warren. One of ordinary skill in the art would have been motivated to utilize such drug carriers for target cell delivery of therapeutic or diagnostic agents because these biocompatible complexes have been shown by Burke et al to enhance delivery of labile drugs to target cells upon administration to an organism compared to drugs administered without protective carrier complexes, providing increased quantities of drugs to the target cell in a biologically active form.

Further, the Examiner stated:

> One of ordinary skill in the art would have expected that biologically compatible nucleotide conjugates are obtained utilizing acetal-containing polymers because nucleotide conjugation to various moieties utilizing acetyl groups have been taught previously by Matysiak, *et al.*, and covalently-linked nucleotide conjugates have been shown to have enhanced biological stability in appropriate biological contexts compared to non-conjugated drug-carriers, as taught previously by Ishihara *et al.*

Also, the Examiner stated that:

> One of ordinary skill in the art would have been motivated to utilize intercalating agents for therapeutic or diagnostic purposes because intercalating agents are known to be successfully delivered to target cells as bioconjugates, as taught previously by Ishihara, *et al.*

The Examiner also stated that the bis-intercalating agent, ditercalinium, has been used as an anticancer drug by inducing DNA repair systems when delivered to target cells, as taught previously by Gao, *et al.*

Applicant's Claims 14-17 and 20-22 are directed to a drug-carrier that includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/liter at 25°C.

As discussed above, there is no disclosure in Warren of a drug-carrier, as set forth in Claims 14-17 and 20-22, that includes a double-stranded nucleotide, and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer has an aqueous solubility of at least one mg/liter 25°C.

Claim 28, as amended, is directed to a drug-carrier complex comprising a single-stranded nucleotide, a drug noncovalently associated with the single-stranded nucleotide and a polymer associated with the single-stranded nucleotide or the drug. Claims 29 and 30 are dependent from Claim 28 and add further limitations that the polymer is covalently associated with the single-stranded nucleotide or the polymer is associated with the drug, respectively.

There is no disclosure or suggestion in Warren of a drug-carrier complex comprising a single-stranded nucleotide, a drug noncovalently associated with the single-stranded nucleotide and a polymer associated with a single-stranded nucleotide or drug, as set forth in Applicant's pending Claims 28-30. As discussed above, the association between the drug and nucleotide of Warren's nucleotide-based prodrugs is a covalent association.

Claim 34, as amended, is directed to a drug-carrier comprising a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, in the polymers have an aqueous solubility of at least one mg/liter at 25°C. Claim 36, as amended, is

directed to a drug-carrier composition comprising a nucleotide component and a drug component noncovalently associated with the nucleotide carrier component, the drug-carrier composition having a moisture content less than about 5% by weight. Claim 37, as amended, is directed to a drug-carrier composition consisting essentially of a drug component noncovalently associated with a nucleotide component.

As discussed above, Warren does not teach or suggest a drug-carrier comprising a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, wherein the polymers have an aqueous solubility of at least one mg/liter at 25°C, as set forth in amended Claim 34. In addition, as also discussed above, Warren does not teach or suggest a drug-carrier composition comprising a nucleotide carrier component and a drug component noncovalently associated with the nucleotide carrier component, the drug-carrier composition having a moisture content less than about 5% by weight, which is the subject matter of Claim 36, as amended. In addition, Warren does not teach or suggest a drug-carrier composition consisting essentially of a drug noncovalently associated with a nucleotide component, as set forth in Claim 37, as amended. Therefore, Warren does not disclose or suggest Applicant's invention as set forth in pending Claims 14-17, 20-22, 28-30, 34, 36 and 37.

Matysiak, *et al.*, teach a method to enhance cellular uptake of antisense oligonucleotides or their analogs by linking them with derivatized cholesteryl-acetals.

Matysiak, *et al.* do not remedy the deficiencies of Warren. Specifically, there is no disclosure or suggestion in Warren, or Matysiak, *et al.*, taken either separately or in combination of a drug-carrier that includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/l at 25°C, as set forth in Applicant's Claims 14-17 and 20-22. In addition, neither Warren, or Matysiak, *et al.*, taken either separately or in combination, disclose a drug carrier complex comprising a single-stranded nucleotide, a drug noncovalently associated with the single-stranded nucleotide and a polymer associated with a single-stranded nucleotide or the drug as set forth in Applicant's Claims 28-30, as amended. There is no disclosure or suggestion in Warren or Matysiak, *et al.*, taken separately or in combination, of a drug-carrier comprising a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, wherein the polymers have an aqueous solubility

of at least one mg/liter at 25°C, as set forth in Applicant's Claim 34, as amended. Further, there is no disclosure or suggestion in either Warren or Matysiak, *et al.*, taken either separately or in combination of a drug-carrier composition comprising a nucleotide carrier component and a drug component, noncovalently associated with the nucleotide carrier component, the drug-carrier composition having a moisture content less than about 5% by weight, as set forth in Applicant's Claim 36, as amended. Moreover, there is no disclosure or suggestion in either Warren or Matysiat, *et al.*, of a drug-carrier composition comprising essentially a drug component noncovalently associated with a nucleotide component, as set forth in Applicant's Claim 37, as amended. Therefore, neither Warren or Matysiak, *et al.*, taken either separately, or in combination, disclose or suggest Applicant's invention as set forth in Claims 14-17, 20-22, 28-30, 34, 36 and 37.

Ishihara, *et al.*, teach amidite derivatives and oligonucleotide derivatives. More specifically, complexes of saccharides and oligonucleotides are disclosed. The saccharide component is employed as a means for delivery of the oligonucleotide in order to affect expression in a cell, such as by delivering an antisense oligonucleotide to suppress expression of a specific gene of a targeted organ. In the background portion of Ishihara, *et al.*, referenced by the Examiner, other combinations of oligonucleotides and compounds, including intercalators, are described. In each embodiment in Ishihara, *et al.*, the oligonucleotide is a "drug," as that term is defined by Applicant in the instant application.

The "drug carriers" of Applicant's invention do not include "a drug" or "drug component" as those terms are defined in Applicant's specification. Rather, the drug-carrying component of "drug-carrier complexes" of Applicant's specification is set forth in the specification at page 13, lines 11-16:

> The term "nucleotide component" refers to the drug-binding (drug carrying) component of the drug-carrier complexes of this invention. The drug-binding component comprises at least one nucleotide strand. The nucleotide component may include or be further associated with, other components (e.g., polymers, oligomers, ligands) to form [a] drug carrier, a drug delivery system, or a drug-laden implant. In one embodiment, the nucleotide strand is an oligonucleotide strand.

As shown at page 13, lines 28 through page 14, line 9 of the Applicant's specification a "drug" as that term is employed by Applicant, refers to therapeutic and diagnostic compounds:

> The term "drug" is used herein interchangeably with the term "drug component." In one embodiment, the drug of the pharmaceutical formulation is a therapeutic drug. The term "therapeutic," when referring to a drug used in the invention, refers to a drug used to treat, remediate or cure a disorder or a disease (e.g., hereditary diseases, viral diseases such as AIDS, cancer). In another embodiment, the drug of the pharmacuetical formulation is a diagnostic drug (e.g., a radioactive diagnostic drug, a fluorescent diagnostic drug, a paramagnetic diagnostic drug, superparamagnetic diagnostic drug, an x-ray dense diagnostic drug or an electron-dense diagnostic drug). The term "diagnostic," when referring to a drug employed in the invention, refers to a drug employed to determine the nature or extent of a disease, or employed to confirm the presence of a disorder or a disease.

Drug carrier compositions, as set forth in Claim 36 and 37, as amended, include a nucleotide carrier component and a drug component which are noncovalently associated with each other.

As with Warren and Matysiak, *et al.,* there is no disclosure or suggestion in Ishihara, *et al.* of Applicant's claimed drug-carrier or drug-carrier complex, as set forth in pending Claims 14-17, 20-22, 28-30, 34, 36 and 37, as amended. Specifically, there is no disclosure or suggestion in Warren, Matysiak, *et al.* or Ishihara, *et al.*, taken either separately or in combination, of a drug-carrier or drug-carrier composition that includes either a drug-carrier component in which the drug component is noncovalently associated with the nucleotide component of the nucleotide-based carrier or that includes a single- or double-stranded nucleotide that is a component of a drug-carrier as opposed to a drug-carrier complex, or as a distinct non-drug component of a drug-carrier complex. Therefore, Applicant's claimed invention, as amended, is not obvious in view of any of these references, taken either separately or in combination.

Gao, *et al.*, teach a combination of a synthetic anticancer drug, ditercalinium, with DNA in a non-covalent complex. The non-covalent DNA-ditercalinium complexes are incorrectly recognized by a uvrABC repair system in procaryotes as covalent lesions on DNA, thereby affecting cellular repair systems of the procaryote.

As with Warren, Matysiak, *et al.*, and Ishihara, *et al.*, there is no disclosure or suggestion in Gao, *et al.* of the subject matter of Applicant's drug-carrier, as set forth in Claims 14-17 and 20-22, which includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/liter at 25°C.

As with Warren, Matysiak, *et al.* and Ishihara, *et al.*, there is no disclosure or suggestion by Gao, *et al.*, that the DNA component acts as a "drug" as that term is defined by Applicant's specification. As stated by Gao, *et al.*, at page 2425:

> The diversity of the covalent damage excised by uvrABC suggests that the DNA distortions are recognized by uvrABC rather than the intrinsic structural motifs of the adducts . . . . To account for uvrABC recognition of such a diverse array of DNA lesions, it has been proposed (1) the uvrABC recognizes DNA kinks and binds to the face of the DNA that does not contain the adduct.

Therefore, as proposed by Gao, *et al.*, the DNA is not the drug component of a drug-carrier that includes a nucleotide and a polymer, as claimed by Applicant. Further, there is no disclosure or suggestion in Gao, *et al.*, of combination of the DNA component with a polymer to thereby form a drug-carrier. Therefore, there also is no disclosure or suggestion of combining a single-stranded nucleotide, a drug that is noncovalently associated with the single-stranded nucleotide and a polymer associated with the single-stranded nucleotide or drug to form a drug-carrier complex, as set forth in Claims 28-30, as amended. As a consequence, Gao, *et al.*, do not remedy the deficiencies of Warren, Matysiak, *et al.*, and Ishihara, *et al.*, taken separately or in combination.

In addition, Gao, *et al.*, also does not remedy the deficiencies of Warren, Matysiak, *et al.*, and Ishihara, *et al.*, in that none of these references, taken either separately or in combination, disclose or suggest a drug-carrier complex comprising a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, wherein the polymers have an aqueous solubility of at least one mg/liter at 25°C, which is the subject matter of Applicant's Claim 34, as amended.

Further, Gao, *et al.*, also does not remedy the deficiencies of Warren, Matysiak, *et al.* or Ishihara, *et al.*, in that none of these references, taken either separately or in combination, disclose or suggest a drug-carrier composition as set forth in Applicant's Claims 36 and 37, as amended, wherein the drug-carrier composition includes a drug component noncovalently associated with a nucleotide carrier component and has moisture content less than about 5% by weight (Claim 36) or a drug-carrier composition consisting essentially of a drug component noncovalently associated with a nucleotide component (Claim 37).

Therefore, Applicant's claimed invention, as amended, is not obvious in view of Gao *et al.*, Warren, Matysiak *et al.*, and Ishihara *et al.*, taken separately or in any combination.

Burke is directed to polymer/drug microparticles. The polymer can be a biocompatible polymer, such as poly(lactic acid-co-glycolic acid). The drug can be a labile drug, such as a protein, or a polynucleotide. The term "drug," as defined by Burke, is set forth at Col. 4, line 57 through Col. 5, line 3:

> As used herein the term "drug"refers to an agent, or its pharmaceutically acceptable salt, which possesses therapeutic, prophylactic or diagnostic properties in vivo. Examples of suitable therapeutic or prophylactic agents which can be labile drugs, include, for example, proteins such as immunoglobulin-like proteins, antibodies, cytokines (e.g., lymphokines, monokines, chemokines), interleukins, interferons, erythropoietin (also referred to herein as "EPO"), nucleases, tumor necrosis factor, colony stimulating factors, insulin, enzymes, tumor suppressors, hormones (e.g., growth hormone and adrenocorticotrophic hormone), antigens (e.g., bacterial and viral antigens), growth factors, peptides, polypeptides, and polynucleotides, such as antisense molecules.

As with Warren, Matysiak, *et al.*, Ishihara, *et al.*, and Gao, *et al.*, there is no disclosure or suggestion in Burke of the subject matter of Applicants' drug carrier, as set forth in Claims 14-17 and 20-22, which includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, the polmer component having a aqueous solubility of at least one mg/liter at 25°C.

In addition, Burke, does not remedy the deficiencies of Warren, Matysiak, *et al.*, Ishihara, *et al.*, and Gao, *et al.*, in a disclosure or suggestion of a drug-carrier complex comprising a

single-stranded nucleotide, a drug noncovalently associated with the single-stranded nucleotide and a polymer associated with the single-stranded nucleotide or the drug, as set forth in Applicant's Claims 28-30. Specifically, there is no disclosure in Burke of a single-stranded nucleotide component distinct from the drug and polymer components of the disclosed polymers/drug matrix particles described in Burke. Rather, the polynucleotides disclosed in Burke are examples of labile drugs which, by definition, possess therapeutic, prophylactic or diagnostic properties *in vivo*. There is no disclosure or suggestion of the presence of a single-stranded nucleotide component of the polymer/drug matrix particles, other than those which are drugs. Therefore, Burke does not disclose or suggest Applicant's invention, alone or in combination with Warren, Matysiak, et al., Ishihara, et al., and Gao, et al., as set forth in Applicant's pending Claims 28-30.

As discussed above, Applicant's claimed drug-carrier as set forth in Claim 34, as amended, including a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, wherein the polymers have an aqueous solubility of at least one mg/liter at 25°C, which is distinct from a "drug" component of a "drug-carrier complex. Further, as discussed above, Applicant's claimed drug-carrier compositions, including the claimed compositions as set forth in Claims 36 and 37, as amended, include a drug component which is distinct from the "drug-carrier of the drug-carrier composition." Therefore, Burke, alone or in combination with Warren, Matysiak, *et al.*, Ishihara, *et al.*, or Gao, *et al.*, does not disclose or suggest Applicant's claimed drug-carrier composition as set forth in Claims 34, 36 and 37, as amended. In addition, there is no disclosure or suggestion in Burke, alone or in combination with Warren, Matysiak, *et al.*, Ishihara, *et al.*, or Gao, *et al.*, of a combination of a polynucleotide and a polymer wherein the polynucleotide is not also a drug.

Taken separately or in combination, Applicant's claimed invention, as set forth in pending Claims 14-17, 20-22, 28-30, 34, 36 and 37 meets the requirements of 35 U.S.C. § 103 in view of Warren, Matysiak, *et al.*, Ishihara, *et al.*, Gao, *et al.*, and Burke taken either separately or in any combination.

SUMMARY AND CONCLUSIONS

The subject matter of pending Claims 14-16, 20-22, 34, 36 and 37 meets the requirement of 35 U.S.C. § 102(b), in view of Warren. Further, pending Claims 14-17, 20-22, 28-30, 34, 36 and 37 meet the requirements of 35 U.S.C. § 103(a), in view of Warren, in further view of Matysiak, *et al*, Ishihara, *et al.* Gao, *et al.*, and Burke, taken either separately or in any combination. Therefore, Applicant respectfully requests reconsideration and allowance of the claims under consideration.

If the Examiner feels that a telephone conference would expedite prosecution of this application, she is invited to call Applicant's undersigned Attorney.

Respectfully submitted,
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